## HIV-INFECTED WOMEN (Updated January 10, 2011)

***Panel's Recommendations:***

- ***The indications for initiation of antiretroviral therapy (ART) and the goals of treatment are the same for HIV-infected women as for other HIV-infected adults and adolescents (AI).***
- ***Women taking antiretroviral (ARV) drugs that have significant pharmacokinetic interactions with oral contraceptives should use an additional or alternative contraceptive method for prevention of unintended pregnancy (AIII).***
- ***In pregnant women, an additional goal of therapy is prevention of mother-to-child transmission (PMTCT), with a goal of maximal viral suppression to reduce the risk of transmission of HIV to the fetus and newborn (AI).***
- ***Genotypic resistance testing is recommended for all HIV-infected persons, including pregnant women, prior to initiation of ART (AIII) and for women entering pregnancy with detectable HIV RNA levels while on therapy (AI).***
- ***When selecting an ARV combination regimen for a pregnant woman, clinicians should consider the known safety, efficacy, and pharmacokinetic data of each agent during pregnancy (AIII).***
- ***Efavirenz (EFV) should be avoided in a pregnant woman during the first trimester or in a woman who desires to become pregnant or who does not or cannot use effective and consistent contraception (AIII).***
- ***Clinicians should consult the most current Health and Human Services (HHS) Perinatal Guidelines when designing a regimen for a pregnant woman (AIII).***

***Rating of Recommendations: A = Strong; B = Moderate; C = Optional***
***Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion***

This section provides discussion of some basic principles and unique considerations to follow when caring for HIV-infected women in general and for pregnant HIV-infected women. Clinicians who provide care for pregnant women should consult the current ***Perinatal Guidelines*** *[1]* for in-depth discussion and management assistance.

### *Gender Considerations in Antiretroviral Therapy*

In general, studies to date have not shown differences in virologic efficacy of ART by gender *[2-4],* although a number of studies have suggested that gender or sex may influence the frequency, presentation, and severity of selected ARV-related adverse events *[5]*. Although data are limited, there is also evidence that women may metabolize and respond to specific medications, including ARV drugs, differently than men *[6-8]***.**

**Adverse Effects**:

- ***Nevirapine (NVP)-associated hepatotoxicity***: NVP has been associated with an increased risk of symptomatic, potentially fatal, and often rash-associated liver toxicity among ARV-naïve individuals; women with higher CD4 counts (>250 cells/mm$^3$) appear to be at greatest risk *[9-12]*. It is generally recommended that NVP not be prescribed to ARV-naïve women who have CD4 counts >250 cells/mm$^3$ unless there is no other alternative and the benefit from NVP outweighs the risk of hepatotoxicity **(AI)**.
- ***Lactic acidosis***: There appears to be a female predominance in the increased incidence of symptomatic and even fatal lactic acidosis associated with prolonged exposure to nucleoside reverse transcriptase inhibitors (NRTIs). Lactic acidosis is most common with stavudine (d4T), didanosine (ddI), and zidovudine (ZDV); however, it can occur with other NRTIs *[13]*.
- ***Metabolic complications***: A few studies have compared women to men in terms of metabolic complications associated with ARV use. HIV-infected women are more likely to experience increases in central fat with ART and are less likely to have triglyceride elevations on treatment *[14-15]*. Women have an increased risk of osteopenia/osteoporosis, particularly after menopause, and this risk may be exacerbated by HIV and ART *[16-17]*. At the present time, none of these differences requires a change in recommendations regarding treatment or monitoring.

### *Women of Childbearing Potential*

All women of childbearing potential should be offered preconception counseling and care as a component of routine primary medical care. Discussion should include special considerations with ARV use when trying to conceive and during pregnancy. (See ***Perinatal Guidelines*** *[1]*). The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans, and use of effective contraception to prevent unintended pregnancy should be discussed with women. As part of the evaluation for initiating ART, women should be counseled about the potential teratogenic risk of EFV-containing regimens, should pregnancy occur. EFV-containing regimens should be avoided in women who are trying to conceive or who are sexually active and not using effective and consistent contraception.

Effective contraception should be available for women who wish to prevent pregnancy. Several protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have drug interactions with combined oral contraceptives (COCs). Interactions include either a decrease or an increase in blood levels of ethinyl estradiol, norethindrone, or norgestimate (see **Tables 15a and b**), which potentially decrease contraceptive efficacy or increase estrogen- or progestin-related adverse effects (e.g., thromboembolic risk). In general, women who are on any of these ARV drugs should use an alternative or additional method of contraception **(AIII)**. Although there is minimal information about drug interactions with use of newer combined hormonal contraceptive methods (e.g., transdermal patch, vaginal ring), an additional or alternative contraceptive method should also be considered on the basis of established drug interactions between ARVs and COCs. Data on drug interactions between ARVs and progestin-only contraceptive methods are limited; however, recent data have found no significant changes in ARV drug concentrations of nelfinavir (NFV), NVP, or EFV when used with depot medroxyprogesterone acetate (DMPA), and there is no evidence of reduced DMPA effectiveness *[18-20]*. Intrauterine devices have been shown to be safe and effective in HIV-infected women *[21-22]*. Counseling about reproductive issues should be provided on an ongoing basis.

### *Pregnant Women*

The use of combination ARV regimens is recommended for all HIV-infected pregnant women, regardless of virologic, immunologic, or clinical parameters, primarily for prevention of HIV transmission from mother to child and for treatment of maternal infection **(AI)**. Pregnant HIV-infected women should be counseled regarding the known benefits versus potential risks of ARV use during pregnancy to the mother, fetus, and newborn. A woman's decision regarding ARV use should be respected. Coercive and punitive policies undermine provider-patient trust and could discourage women from seeking prenatal care and adopting health care behaviors that optimize maternal, fetal, and neonatal well-being.

**Prevention of Mother-to-Child Transmission (PMTCT).** Both reduction of HIV RNA levels and use of ARVs appear to have an independent effect on reduction of perinatal transmission of HIV *[23-25]*. The goal of ARV use is to achieve maximal and sustained suppression of HIV RNA levels during pregnancy, but most critically by late pregnancy and the time of delivery, when most transmission occurs.

Genotypic resistance testing is recommended for all pregnant women prior to ARV initiation **(AIII)** and for women entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**. Optimal prevention of perinatal transmission may require initiation of ARV before results of resistance testing are available. If results demonstrate the presence of significant mutation(s) that may confer resistance to the prescribed ARV regimen, the regimen should be modified.

Long-term follow-up is recommended for all infants born to women who have received ARVs during pregnancy, regardless of the infant's HIV status.

**Regimen Considerations.** Pregnancy should not preclude the use of optimal drug regimens. However, recommendations regarding the choice of ARVs for treatment of HIV-infected pregnant women are subject to unique considerations, which may result in different specific recommendations regarding timing of initiation and choice of drugs. These considerations include the following:

- potential changes in pharmacokinetics, and thus dosing requirements, which result from physiologic changes associated with pregnancy,
- potential ARV-associated adverse effects in pregnant women,
- effect on the risk of perinatal transmission of HIV, and
- potential short- and long-term effects of the ARV on the fetus and newborn, which are unknown for many drugs.

Clinicians should review the ***Perinatal Guidelines*** *[1]* for a detailed discussion of drug choices. Combination drug regimens are considered the standard of care in pregnancy, both for the treatment of HIV infection and for PMTCT. ZDV by intravenous infusion to the mother during labor and orally to the neonate for 6 weeks is recommended irrespective of antenatal regimen chosen.

There are some specific differences in treatment recommendations in pregnancy based on the above considerations.

**NRTIs:**

- Although no longer considered a preferred NRTI for non-pregnant adults and adolescents, ZDV is still one of the preferred NRTI drugs when used in pregnancy based on long-term effectiveness in prevention of transmission and safety data in pregnancy (for more detailed discussion, see the ***Perinatal Guidelines*** *[1]*). However, ZDV should not be included in a regimen if there is severe toxicity, documented resistance, or if the woman is also receiving d4T. Women already on a fully suppressive regimen that does not include ZDV should continue on the regimen **(AIII)**.
- The syndrome of lactic acidosis and hepatic steatosis may present with similar signs and symptoms to certain pregnancy-specific disorders (i.e., acute fatty liver of pregnancy, HELLP [hemolysis, elevated liver enzymes, low platelet count] syndrome). Given this similarity, clinicians should have a low threshold for considering lactic acidosis in the differential diagnosis and for appropriate evaluation of pregnant HIV-infected women receiving NRTIs with a consistent clinical picture, particularly if they have accompanying hepatitis or pancreatitis.

**NNRTIs:**

- EFV-containing regimens **should be avoided** in the first trimester, because significant teratogenic effects were seen in primate studies at drug exposures similar to those achieved during human exposure **(AIII)**. In addition, several cases of neural tube defects have now been reported after early human gestational exposure to EFV *[26-27]*. EFV may be considered for use after the first trimester if indicated because of toxicity, resistance, drug interaction issues, or other clinical concerns (e.g., adherence, presentation after first trimester on EFV-containing regimen) *[28]*.
- Although there is no evidence that pregnancy additionally increases risk of NVP toxicity over that in nonpregnant women *[29]*, NVP should not be initiated as a component of a combination regimen in ARV-naïve pregnant women who have CD4 counts >250 cells/mm$^3$ unless the benefit clearly outweighs the risk **(AII)**.

**PIs:**

- Several small studies show that optimal levels of several PIs may not be achieved in pregnancy with standard dosing, especially in the third trimester, although the clinical relevance of this is unknown *[30-32]*. For more information regarding potential dosing alterations, please refer to the ***Perinatal Guidelines*** *[1]*. Once-daily lopinavir/ritonavir (LPV/r) dosing is not recommended in pregnancy, because there are no data to address adequacy of blood levels with this dosing regimen **(BII)**.

Minimal data exist on the use of newer agents, including entry inhibitors and integrase inhibitors, in pregnancy.

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to ARVs (either administered alone or in combinations) to the Antiretroviral Pregnancy Registry (**http://www.apregistry.com**). The registry collects observational data regarding exposure to FDA-approved ARV drugs during pregnancy for the purpose of assessing potential teratogenicity. For more information regarding selection and use of ART during pregnancy, refer to the ***Perinatal Guidelines*** *[1]*. Lastly, women should be counseled regarding the avoidance of breastfeeding. Continued clinical, immunologic, and virologic follow-up should be done as recommended for nonpregnant adults and adolescents.

### *Discontinuation of Antiretroviral Therapy Postpartum*

Following delivery, considerations regarding continuation of ART for maternal therapeutic indications are the same as for other nonpregnant individuals. The decision of whether to continue therapy after delivery should take into account current recommendations for initiation of ART, current and nadir CD4 T-cell counts and trajectory, HIV RNA levels, adherence issues, and patient preference. A study from the Women and Infants Transmission Study (WITS) of women who were ARV naïve prior to pregnancy and had CD4 counts >350/mm$^3$ *[33]* found no significant differences in CD4 count, viral load, or disease progression among those who did or did not continue ART after delivery through 12 months postpartum. In most cases, when drugs are discontinued postnatally, all drugs should be stopped simultaneously. However, if therapy includes an NNRTI, stopping all regimen components simultaneously may result in functional monotherapy because of the long half-life of the NNRTI, which may increase risk of resistance. In one study, NVP resistance was identified in 16% of women on an NVP-containing regimen despite continuation of the NRTI backbone for 5 days after stopping NVP *[34]*. For women whose antepartum regimen included an NNRTI and who plan to stop ARV prophylaxis after delivery, consideration should be given to stopping the NNRTI and continuing the other ARV or switching from an NNRTI to a PI prior to interruption and continuing the PI with the other ARV for a period of time before electively stopping ART. The optimal interval between stopping an NNRTI and the other ARV is not known; at least 7 days is recommended but some experts recommend continuing the other ARV or substituting a PI plus two other agents for up to 30 days. Additional research is needed to assess appropriate strategies for stopping NNRTI-containing combination regimens after delivery in situations when ongoing maternal treatment is not indicated and to assess the effect of limited-duration, fully suppressive ARV prophylaxis in pregnancy on future treatment efficacy. (See **Discontinuation or Interruption of Antiretroviral Therapy**.)

In HIV and hepatitis B virus (HBV) coinfected pregnant women who are receiving ART only for perinatal prophylaxis and who are stopping therapy after delivery, careful clinical and laboratory monitoring for HBV flare should be performed postpartum when ARVs active against HBV are discontinued. However, if treatment for HBV is indicated, a full combination regimen for both HIV and HBV infection should be continued. (See **Initiating Antiretroviral Therapy**.)

## References


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